Aventis Pharmaceuticals

Aventis

11 January, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

COMMENTS on DRAFT GUIDANCE
Development of Antimicrobial Drug Products
Docket No. 99D-4328

Dear Sir or Madame,

Enclosed are two copies of comments from Aventis Pharmaceuticals on the Draft Guidance for Industry on Developing Antimicrobial Drug to Treat Catheter-Related Bloodstream Infections (Docket No. 99 D-4328).

Although the deadline published in the 21 October, 1999 Federal Register was noted as 20 December, 1999; during a phone conversation on 15 December, 1999 between Donald Jaffe (Industry Representative for PhRMA) and Dr. Renata Albrecht, Dr. Albrecht agreed to accept comments in January, 2000.

Thank you for considering these comments during the development process.

Please contact me (610-454-5471) or Ms. Mary Elicone (610-454-5859) if any further clarification is needed.

Sincerely yours,

John J. Savarese, MD, PhD
Director, Regulatory Affairs

JJS/MEE/mee
Attachment

99D-4328

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Aventis Comments

Guidance for Industry
Catheter-Related Bloodstream Infections - Developing Antimicrobial Drugs for Treatment

III.C. 1. General Study Characteristics (page 3)
Two equivalence trials or one superiority trial is required. The agency should consider allowing one equivalence trial provided supporting evidence is also submitted. This is similar to the requirements for skin and skin structure infections, febrile neutropenia, and urinary tract infections. Supporting evidence could include demonstration of efficacy in patients with secondary bacteremia due to the same organisms.

III.D. Inclusion Criteria (page 8)
Clinical criteria:
- Definition of tachycardia should be changed to "Pulse rate > 90 bpm."

Microbiologic criteria:
- ratio for paired quantitative cultures should be 5:1;
- criteria using Maki technique should be > 15.

III.E. Exclusion Criteria (page 10)
Patients with renal or hepatic dysfunction should not be excluded, unless pharmacokinetics of one or more study drugs is altered in these patients and dose adjustment is not permitted.

III.G. Evaluation Visits (page 12)
Blood cultures should not be required in all patients at the test-of-cure and late follow-up visits. The incidence of true bacteremia in afebrile patients is very low. We suggest that these cultures be required only in those patients meeting one or more of the following criteria:

- have a temperature > 38°C;
- have persistent signs of infection at the catheter site;
- might have recurrent infection without a clinical manifestation such as fever (i.e., patients on steroids or with renal failure).

III.H. Outcome (pages 13 and 14)
Modified Intent-to-Treat Population:
- The Sponsor feels strongly that very few patients should be excluded from this population. The current criteria are too strict, and if followed, it is likely that only 20% of enrolled patients will be included in this population. Many patients will be enrolled empirically before results of blood and catheter cultures are obtained. In some patients, the catheter may not be removed, which will make it very difficult to confirm the source of the bacteremia as the catheter. In addition, some patients will be enrolled after having received several doses of an antibiotic, and blood cultures may be negative. Thus, we propose that this population not be restricted to patients meeting the strict microbiologic criteria defined on page 9, but should include all patients who meet the clinical criteria and have no other apparent source of the infection.

Evaluable Population

- The Sponsors feels that the microbiologic criteria are too strict, and would only permit approximately 20% of patients to be evaluable. We propose that patients who meet the criteria for bacteremia be included, provided they meet the clinical criteria and have no other apparent source of the infection.
- There is a discrepancy in the criteria for compliance. In this section, it says that 80% of the study regimen must have been given for at least 48 hours. On page 11, under duration of therapy, it says that 80% of the intended regimen be given for at least 72 hours. Moreover, both of these criteria differ from other draft guidances. For example, for prostatitis, at least 80% of doses is required, but no minimum number of days are given. For nosocomial pneumonia, it says that "patients should complete a full course of therapy." We feel that 72 hours may be too short, especially for *S. aureus*, and suggest that this criteria be revised to "80% of the intended regimen".
- Patients who do not complete the late follow-up visit should not *a priori* be excluded from the evaluable population, especially if they were failures at a previous visit.

Cure, Failure Definitions

- To be consistent with our comment above regarding follow-up blood cultures, "negative blood cultures" should be changed to "blood cultures were known or presumed to be negative."
- "Clinical deterioration or relapse while on therapy..." should be changed to "Clinical deterioration or relapse while on therapy or at any time prior to the test of cure visit...."
- Patients with late metastatic sequelae should not be classified as a failure for treatment of catheter-related bacteremia. This should be a secondary outcome category.

III.I. Statistical Considerations

In equivalence trials, the number of patients needed to assess the efficacy of a new treatment with a comparator is highly sensitive to the choice of delta. For instance, a change in the delta criteria from 20% to 10% results in a four-fold increase in the sample size needed to achieve a given statistical power. Such an increase would cause many clinical development programs to become unfeasible to sponsors, resulting in fewer useful agents being made available to treat patients. For a clinical program consisting of two pivotal equivalence trials, the necessity that both criteria listed in the draft guidelines be met in order to justify the choice of delta is too strict - in particular the second one. Our literature searches have not found any recent studies in this population where success rates with line removal alone have been quoted. The likelihood that such published results exist, especially with the additional requirement that line removal practices be similar to those we allow in our trials, seems very remote. The paucity of published results in this population thus makes meeting the second criteria excessively problematic. This guidance on the determination of delta lacks flexibility.

Under the two-equivalence trial requirement proposed in the draft guidance, the probability of an agent achieving the equivalence criteria in both trials despite its true efficacy being 10% less than its comparator is very small. For instance, using a delta of 20%, a true comparator success rate of 70%, and a true treatment rate of 60%, the probability is only 12% that observed results would meet the equivalence criterion in both trials. Using a delta of 15%, this probability becomes 3%. Thus the risk of approval of inferior agents is already sufficiently small.

The 1992 "Points to Consider" document suggests delta values depending on the highest response rate observed in the trial. The PTC suggestions do not materially increase the relative risk in the patient population. This can be seen by first comparing odds ratios (OR) which reflect the relative "burden" between two treatments - that is, the burden from a decrease in the success rate multiplied by the burden from an increase in the failure rate (where OR=1 for perfect equivalence). For instance, if a delta of 10% is used for a study of two highly effective anti-microbials, and the results show a 95% success rate for the control and an 85% rate for the new treatment, this reflects a tripling of the failure rate, with an OR of 0.30; using a 15% delta and results of 85% and 70% for control and new treatments, the OR only increases to 0.41; for 20% delta and success rates of 75% and 55%, the OR is also 0.41. This increase in burden is very modest, and indicates that larger deltas for lower response rates do not put the patient population at heightened risk.

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